Neurofeedback-mediated self-regulation of the dopaminergic midbrain

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Abstract: The dopaminergic system is involved in reward encoding and reinforcement learning. Dopaminergic neurons from this system in the substantia nigra/ventral tegmental area complex (SN/VTA) fire in response to unexpected reinforcing cues. The goal of this study was to investigate whether individuals can gain voluntary control of SN/VTA activity, thereby potentially enhancing dopamine release to target brain regions. Neurofeedback and mental imagery were used to self-regulate the SN/VTA. Real-time functional magnetic resonance imaging (rtfMRI) provided abstract visual feedback of the SN/VTA activity while the subject imagined rewarding scenes. Skin conductance response (SCR) was recorded as a measure of emotional arousal. To examine the effect of neurofeedback, subjects were assigned to either receiving feedback directly proportional (n=15, veridical feedback) or inversely proportional (n=17, inverted feedback) to SN/VTA activity. Both groups of subjects were able to up-regulate SN/VTA activity initially without feedback. Veridical feedback improved the ability to up-regulate SN/VTA compared to baseline while inverted feedback did not. Additional dopaminergic regions were activated in both groups. The ability to self-regulate SN/VTA was differentially correlated with SCR depending on the group, suggesting an association between emotional arousal and neurofeedback performance. These findings indicate that SN/VTA can be voluntarily activated by imagery and voluntary activation is further enhanced by neurofeedback. The findings may lead the way towards a non-invasive strategy for endogenous control of dopamine.

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Neurofeedback-mediated self-regulation of the dopaminergic midbrain

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46 Keywords: real-time fMRI, dopamine, substantia nigra, neurofeedback, skin
47 conductance response

1 Introduction

The mesencephalic dopaminergic brain regions, mainly substantia nigra (SN) and ventral tegmental area (VTA), are involved in various cognitive, motor and emotional functions, namely decision making (Pessiglione et al. 2006), reinforcement learning (Schultz, 1998), movement execution and motor skill learning (Reynolds et al., 2001, Flöel et al., 2005, Molina-Luna et al., 2009, Hosp et al., 2011). A dysfunction of these regions occurs in Parkinson's and related disorders as well as in various psychiatric conditions (Davis et al. 1991). Dopaminergic drugs may have beneficial effects temporarily, but lead to negative side effects after long-term use (Goodwin, 1971). As such, a reliable, non-invasive strategy for modulating the activity of these regions could be of great clinical and scientific value.

The substantia nigra and ventral tegmental area complex (SN/VTA) contains the highest concentration of dopaminergic neurons in the human brain (Francois et al., 1999). Neural activity in this region has been equated with dopamine release (Schultz, 1986) and identified as the source of the nigrostriatal, mesolimbic and mesocortical dopaminergic pathways. We group these two regions together since, in primates, their functions are very similar (Düzel et al., 2009).

Dopaminergic neurons that form the origin of the mesolimbic and mesocortical pathways fire if an unexpected reward occurs. Firing is modulated by the (inverse) variance of the probability of its occurrence (Schultz et al., 1997, Hollerman and Schultz, 1998, Fiorillo et al., 2003, Bayer and Glimcher, 2005, Tobler et al., 2005, Friston et al., 2012). Other studies have also found activation of SN/VTA during pleasant visual (Lane et al., 1997), erotic stimuli (Redouté et al., 2000, Arnow et al., 2002, Stark et al., 2005, Paul et al., 2008) or romantic love (Bartels and Zeki, 2004,

Aron et al., 2005). Hence, imagery of romantic love or other pleasant scenes could be one strategy to up-regulate SN/VTA.

Endogenous regulation of neural activity through biofeedback (visualization of neural activity is known as neurofeedback) has been accomplished using invasive (Fetz, 1969) and non-invasive recordings (Birbaumer et al., 1990). Real-time functional magnetic resonance imaging (rtfMRI) neurofeedback can substitute direct recording of brain activity and is specifically suited to non-invasively access deep brain structures. A number of studies have shown self-regulation of functions in specific brain areas by changes in the BOLD signal, including the anterior cingulate cortex (deCharms et al., 2005), inferior frontal gyrus (Rota et al., 2009), amygdala (Posse et al., 2003), anterior insula (Caria et al., 2007), premotor cortex (Sitaram et al., 2012) and the limbic system (Sitaram et al., 2011) using operant conditioning techniques (for reviews, see (deCharms, 2008, Sitaram et al., 2009, Weiskopf, 2011)).

In this study, we examined the feasibility of endogenous up-regulation of SN/VTA and the potential beneficial effects of neurofeedback in this regard. We additionally investigated the likelihood that the up-regulation activated dopaminergic pathways and finally whether any learning was evident within a single session. The implications of such self-regulation apply to treatment of various neurological and psychiatric disorders.

2 Methods

2.1 Experimental Setup

Thirty-two healthy male subjects, aged between 24-35 years, participated in this experiment, conducted according to the requirements of the Zurich Cantonal Ethics Commission (KEK 2010-0190). Each subject participated in the experiment in a single session in a Philips Achieva 3.0T magnetic resonance (MR) scanner with an eight channel SENSE head coil (Philips, Best, The Netherlands) at the Laboratory for Social and Neural Systems Research (SNS), Zurich. MR-compatible electrocardiogram (ECG), respiration and skin conductance (PowerLab 4/25T and Chart v5.5.2, ADInstruments, Bella Vista, Australia) measurements were collected from each participant. Individual brain volumes were converted from Philips PAR/REC format to ANALYZE DRIN using software from Philips and then placed on a server in real time. A laptop running Turbo BrainVoyager v3.0 (TBV - Brain Innovation, Maastricht, The Netherlands) extracted the BOLD signal from these files, and redirected to provide visual feedback of neural activation using custom-made software on the same laptop with Visual Studio 2008 (Microsoft, Redmond, WA, USA). Subjects viewed visual feedback through a mirror mounted on the head coil reflecting a back-projected display behind the bore.

2.2 Instructions

Participants were instructed to attempt to gain self-control over the region of the brain activated by novel rewarding stimuli. Examples of rewards, such as food, romantic or sexual imagery, time with family and friends, and achievements were suggested. After our pilot studies had shown that romantic or sexual imagery was most effective in volitionally controlling the BOLD signal in the SN/VTA, participants were informed

of these results but allowed to adapt their strategy according to neurofeedback success. Participants were asked to maximize the height of a vertically moving ball on the screen, representing their brain activity, when cued, and informed that the scanner acquisition time as well as the hemodynamic effects would cause approximately five seconds of delay between thought and the feedback signal. Participants were also asked not to move or change their breathing rate consciously, and especially not to change breathing as a strategy to self-regulate the feedback signal. Subjects were informed that they could stop the experiment at any time by pressing a pneumatic button.

2.3 Sequence

Anatomical data were acquired with an ultrafast gradient echo T1-weighted sequence in 301 sagittal plane slices of 250 x 250 mm^2 resulting in 1.1 mm^3 voxels, lasting approximately 5 minutes. The images were then transformed to 1 mm^3 voxel representations and in a standard sagittal plane orientation by BrainVoyager QX v2.3 (Brain Innovation, Maastricht, The Netherlands). Functional data were acquired in 27 ascending transverse plane slices using a gradient-echo T2*-weighted echo-planar image sequence over the whole brain. Acquired in-plane resolution was 2 x 2 mm^2, 3 mm slice thickness and 1.1 mm gap width over a field of view of 220 x 220 mm^2, a TR/TE of 2000/35 ms and a flip angle of 82°. Slices were aligned with the anterior-posterior commissure and elevated by 15 degrees. A single volume was first obtained to help TBV with online coregistration specific for Philips scanners. Five runs of 185 volumes were acquired afterwards.

142 *2.4 Protocol*

143 We used an anatomical localizer to identify the SN/VTA. The spatial extent of the
144 SN/VTA was selected based on previous research (D'Ardenne et al., 2008, Düzel et
145 al., 2009). The caudal edge of the SN was delineated by the cranial edge of the pons
146 at the midline. The cranial border of the region coincided with the cranial border of
147 the tegmentum, measured from the midline, representing the height of the midbrain.
148 VTA was determined by the anterior connection between the two lateral SN
149 structures. Both the SN and VTA were combined into a single anatomical region of
150 interest (ROI) and automatically coregistered with the functional scans in TBV during
151 the neurofeedback runs (Figure 1). Participants received visual feedback of the
152 SN/VTA BOLD signal in the form of a vertically moving ball with written instructions.
153 When “Happy Time” was displayed on the screen, subjects were asked to raise the
154 position of the ball on the screen with a smiley face as high as possible using
155 rewarding mental imagery (Figure 2). Position and color of the ball were proportional
156 to the BOLD signal extracted by TBV. As the ball was climbing, its color gradually
157 changed from red to yellow. When “Rest” was displayed, participants were asked to
158 perform neutral imagery such as mental arithmetic or paper writing, thereby reducing
159 the height of the ball and making it redder in color. The BOLD signal of the SN/VTA
160 region of interest that determined the elevation of the ball, was first normalized based
161 on the percent signal increase from the previous baseline condition (last five
162 volumes), then three-point averaged (i.e. averaging the current value with the
163 previous two) to reduce noise.

164

165 Groups were defined by the type of visual feedback presented in the neurofeedback
166 condition. In the veridical feedback group (15 subjects), elevation of the ball and

change in its color from red to yellow was proportional to the BOLD signal in the ROI. As feedback may act as a reward signal that could independently stimulate SN/VTA, we used a control group (inverted feedback) of 17 subjects to separate the recruitment of SN/VTA due to feedback from its recruitment through mental imagery. In this group, participants were given the same instructions, hence, they used the same imagery to raise the ball. But, the feedback that they received was inverted: the elevation of the ball decreased and its color became red as the SN/VTA BOLD signal increased. Inverted feedback subjects were not made aware of this inverse proportional relationship, and we confirmed that these subjects remained unaware of this relationship in a post-experimental debriefing. In this manner, any differences between the performance of the two groups is caused by the information provided by the neurofeedback. Other control conditions were initially investigated, specifically yoked sham feedback (deCharms et al., 2005), but some subjects were able to identify the non-contingency of the feedback during the experiment and thus this strategy was abandoned.

Each subject underwent five runs with approximately two minutes rest in between. Each run comprised nine blocks of alternating "Rest" (20 s) and "Happy Time" (20 s), totaling about six minutes (Figure 2). Ten seconds were added to the initial rest block to allow enough time to load the initial parameters to TBV. In the first and last runs (i.e. baseline and transfer runs), only instructions were provided with no feedback. Following the baseline run, the next three runs provided feedback of BOLD signal to the participants. To explore whether subjects had learned to self-regulate SN/VTA activity without feedback, the transfer run only showed the instructions. Following the

191 experiment, subjects were asked to report whether they remained with the initial
192 suggested mental strategy, and if not, what strategy they found most useful.

193

194 *2.5 Data Postprocessing and Statistical Tests*

195 Offline preprocessing of functional data was performed using BrainVoyager QX v2.6.
196 Data were slice-time corrected using cubic spline interpolation, motion-corrected with
197 sinc interpolation, and then temporally high-pass filtered using a discrete cosine set
198 of three sines/cosines. Data were coregistered with the subject's own anatomical
199 image. Correction for physiological noise was performed by RETROICOR (Glover et
200 al., 2000) using Fourier expansions of different order for the estimated phases of
201 cardiac pulsation (3rd order), respiration (4th order) and cardio-respiratory
202 interactions (1st order) (Harvey et al., 2008). The corresponding confound regressors
203 were created using a custom in-house Matlab (version R2011a) implementation
204 (Kasper et al., 2009) .

205

206 In first level analysis of functional data, a standard general linear model (GLM)
207 analysis was used. The design matrix included head movement regressors and
208 additional regressors based on the aforementioned RETROICOR analysis. The
209 percent-transformed, mean-corrected beta values from the predefined subject-
210 specific SN/VTA ROI were extracted through BrainVoyager QX. Beta values in
211 BrainVoyager represent the parameter estimates for the task regressor subtracted by
212 a constant representing the mean whole brain parameter estimate. Skin conductance
213 response (SCR) was de-trended and down-sampled to 10 Hz using SCRalyze (Bach
214 et al., 2009). After fitting to a GLM based on task onset, beta values of the SCR data

were extracted from each run. The skin conductance data of two subjects in the veridical feedback group were excluded due to experimenter error.

Second-level analysis of beta values in baseline runs were compared using one-sample t-tests to compare to zero, and two-sample t-tests to compare between groups. Beta values during neurofeedback runs were first subtracted from subject-specific baseline values (thus baseline-corrected), and then input into a 2x3 mixed effects repeated measures analysis of variance (ANOVA) over the three neurofeedback runs. Run number (three levels) was the random effect and group (two levels) was the fixed effect. One-sample t-tests of SN/VTA beta values during transfer runs of each group were used to determine difference from zero, and baseline-corrected beta values were used to compare between groups in a two sample t-test. Analysis of Covariance (ANCOVA) was used to determine whether the covariation between SCR and SN/VTA beta varied between groups. We used SPSS v19 (IBM, Armonk, NY) for all aforementioned statistical tests. Voxel-wise random effects group analysis of neurofeedback runs was performed first by coregistering functional data to Talairach-transformed anatomical images (Talairach and Tournoux, 1988). We used a summary statistic random effects approach where t-tests were applied to first-level contrast images to determine significance within or between conditions. Images were corrected for multiple comparisons using a false discovery rate of $p<0.05$. Active regions were identified based on the nearest coordinate using a Talairach Daemon (Lancaster et al., 2000). Voxel-wise analysis focused on caudate nucleus (Strafella et al., 2001), putamen (York, 1970), nucleus accumbens (Salamone and Correa, 2002), hippocampus (Rossato et al., 2009), amygdala (Wilson et al., 1994), subthalamic nucleus (Limousin et al., 1998) and prefrontal

cortex (Williams and Goldman-Rakic, 1995) – all brain regions with presumed involvement in reward processing.

We also conducted a functional connectivity analysis using the BrainVoyager QX plugin. The seed region (SN/VTA) was anatomically defined as described above, but based on the average Talairach-transformed anatomical scans of all subjects instead of subject-specific scans. The first and last five volumes were excluded. Second level analysis was performed using t-tests. Correction for multiple comparisons was performed at the cluster level. Assuming contiguous clusters rather than individual voxels, Monte Carlo simulations in BrainVoyager were used to adjust for false positives on a cluster level (Forman et al., 1995). We first set the statistical threshold of the contrast to $p<0.05$, then conducted simulations over 1000 iterations, using a cluster-level threshold of $p<0.05$.

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Gelöscht: Talairach

Andreas Luft 13.1.13 13:56
Kommentar [1]: I don't understand.

3 Results

3.1 ROI Analysis

Both groups showed an increase in SN/VTA activity during baseline (see Figure 3 for representative raw data from both groups). The veridical feedback group mean beta values (mean difference = 0.19, $t(14)=5.96$, $p<10^{-4}$) during baseline were slightly less than the inverse feedback group (mean difference = 0.20, $t(16) = 3.69$, $p<0.005$). However, this difference was not significant (mean difference = -0.01, $t(30)=-0.22$, $p = 0.83$).

During neurofeedback, repeated measures ANOVA revealed an overall increase in SN/VTA activity compared to baseline in the veridical feedback group, as expressed by the intercept ($F(1) = 8.54$, $p<0.05$), with a significant increase between the first and second neurofeedback runs ($F(2,13)=4.26$, $p<0.05$). In contrast, the inverted feedback group showed neither an overall change in baseline-corrected SN/VTA activity ($F(1) = 1.46$, $p=0.24$), nor a difference between runs ($F(2,15)= 1.50$, $p = 0.26$). Between the two groups, there was a significant interaction between group and run ($F(2,29)= 4.80$, $p<0.05$), driven by higher SN/VTA activity in the second neurofeedback run in the veridical group compared to the inverted group. Figure 4 shows the baseline-corrected SN/VTA beta values over all runs for both groups.

In transfer, both groups showed overall increases in SN/VTA activity, with the veridical group (mean difference = 0.20, $t(14)=4.40$, $p<0.001$) slightly higher than the

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Kommentar [2]: What does this statistic refer to?

inverted group (mean difference = 0.18, t(16) = 3.21, p<0.01). When corrected for baseline performance, however, there was no change in the veridical (mean difference = 0.03, t = 0.64, p = 0.53), or inverted (mean difference = -0.02, t= -0.33, p = 0.75) feedback groups, nor a difference between them (mean difference = 0.05, t(30) = 0.64, p=0.53).

3.2 Random Effects Group Analysis

In a secondary voxel-wise analysis, we investigated the specificity of neurofeedback. In the veridical feedback group we found activation of reward-related regions when comparing neurofeedback to rest. Both groups showed significant activation in SN/VTA, caudate body (Ca), hippocampus (Hi) and nucleus accumbens (NAcc) (Table 1 and Figure 5). There were no significant differences found between groups.

3.3 Functional Connectivity Analysis

Both groups also showed increased functional connectivity of the SN/VTA with reward regions. As shown in Figure 6 and Table 2, the veridical feedback group showed increased connectivity in left NAcc and Putamen (Pu), whereas in the inverted feedback group showed increased connectivity in bilateral Ca and Pu. Comparing both groups, the veridical feedback group had greater connectivity than the inverted feedback group in the Ca.

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Kommentar [3]: same

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Kommentar [4]: This, you need to explain a bit further.

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Kommentar [5]: "Connectivity in" is confusing. Connectivity is always between areas, correct? Should be between SN/VTA and NAcc, Pu resp.

3.4 Behavioral Measures

To account for inter-subject variations in performance, we acquired an independent measure of attention and emotional arousal (skin conductance response, SCR, for review see (Critchley, 2002)). There was no significant change in baseline-corrected beta values of SCR for either the veridical ($F(1)= 1.85$, $p= 0.20$) or inverted ($F(1) = 0.04$, $p = 0.85$) feedback groups, nor within runs ($F(2,11) = 2.45$, $p = 0.13$), $F(2,15) = 0.50$, $p = 0.62$), or between groups ($F(2,27) = 1.42$, $p = 0.32$). However, the correlation between pooled beta values for SCR and SN/VTA activity showed a significant difference between groups ($F(1) = 5.00$, $p<0.05$, see Figure 7). This difference was driven by a positive trend in the veridical feedback group ($r = 0.45$, $p= 0.12$) and a negative trend in the inverted feedback group ($r = -0.35$, $p = 0.18$).

The groups also differed in their chosen imagery strategy, despite both groups being given the same instructions. In the veridical feedback group, all 15 subjects reported that their best mental strategy was sexual or romantic imagery, whereas in the inverted feedback group, six out of 17 reported that their best strategy was something other than the suggested imagery strategy. The alternate strategies were sports, holidays, family, friends, academic success and travelling (one subject used each strategy). Strategy did not correlate with the ability to self-regulate SN/VTA (binary logistic regression, $p=0.29$).

4 Discussion

The primary goal of this study was to investigate whether one can self-regulate the SN/VTA activity and if so, if neurofeedback can assist. We found that participants were able to increase the activity in the region during the baseline condition without feedback. Subjects with veridical feedback improved the ability to up-regulate SN/VTA, co-activated other dopaminergic regions, and showed increased connectivity along the nigrostriatal pathway compared to controls. Behavioral measures such as SCR correlation with SN/VTA and chosen imagery strategy also differed between groups, further showing the beneficial effect of veridical neurofeedback.

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The first aim of this investigation was to determine whether any mental strategy could consistently up-regulate the SN/VTA. We built upon previous research of visual presentation of pleasant, erotic or romantic scenes to evoke activity in this region (Lane et al., 1997, Arnow et al., 2002, Bartels and Zeki, 2004, Aron et al., 2005). In this study, both groups showed increased SN/VTA activity using mental imagery of sexual and romantic scenes instead of explicit visual stimulation. These results suggest that such rewarding imagery is a robust method of SN/VTA self-up-regulation. To our knowledge, this is the first evidence of endogenous (i.e. without external stimulation) up-regulation of SN/VTA.

More interestingly, our results show that veridical neurofeedback positively affects control of SN/VTA. The veridical feedback group had significantly increased SN/VTA

activity during neurofeedback compared to baseline whereas the inverted feedback group did not. Additionally, the veridical feedback group showed significantly higher activity in the second run than the inverted feedback group. We additionally found increased functional connectivity in the dorsal striatum in the veridical feedback group compared to controls, indicating an advantageous effect of veridical neurofeedback within the nigrostriatal pathway. We expected a significant drop in the inverted feedback group, but instead observed a non-significant decreasing trend. We attribute this to the instructed explicit rewarding mental imagery strategy in opposition to the feedback.

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Kommentar [6]: I thought you found increased connectivity between ventral striatum (NAcc) and SN/VTA as well as dorsal striatum (Pu). That would argue for an upregulation of both mesolimbic and nigrostriatal pathways.

Behavioral evidence also indicates a positive effect of veridical neurofeedback on SN/VTA up-regulation. There was a difference in emotional arousal due to the type of feedback provided, as the correlation between ability to self-regulate and SCR beta values was significantly different between the groups. It is notable that despite being given identical instructions, all of the subjects in the veridical feedback group remained with the suggested strategy, whereas over a third of the inverted feedback group found other strategies more effective. Taken together, results strongly suggest that neurofeedback does play a role in facilitating self-regulation of SN/VTA.

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There is mixed evidence to suggest a learned ability to self-regulate SN/VTA was obtained in a single session. There was an increased SN/VTA activity in the veridical feedback group in the second run, but this improvement reduces in the third run (albeit not significantly), and was no different than the control group. In addition, there was no significant increase in transfer compared to baseline. Whether this drop

in performance later in the session was a consequence of habituation (attenuation) or cognitive fatigue remains to be investigated. Indeed, cognitive fatigue-related regions such as the cerebellum, cingulate cortex, insula, and lingual gyrus were activated (Cook et al., 2007, DeLuca et al., 2008). Since disruption of SN/VTA activity is a neural mechanism of central fatigue (for review, see (Chaudhuri and Behan, 2000)), it is possible that SN/VTA self-regulation could have an interactive effect.

Hemodynamic delay could additionally impair learning, but this is unlikely given the greater learning earlier in the session instead of later. Additionally, there is strong evidence showing that feedback delays can be overcome when consistent (Miall et al., 1993). Learned self-regulation has been achieved using rtfMRI neurofeedback with delays as long as 60 seconds (Yoo and Jolesz, 2002). Perhaps the most likely explanation for the performance drop is habituation. It is well known that the SN/VTA responds to novel rewards (Schultz, 1998, Bunzeck and Düzel, 2006), and after a 30-minute succession of trials, self-generation of novel rewards likely becomes increasingly difficult. Veridical feedback may have postponed this drop due to a novel feedback experience introduced by the correlation between activation and elevation of the ball.

Whether or not the increase in BOLD signal in SN/VTA reflects the activity of dopaminergic neurons cannot be directly answered with fMRI, although activity found within dopaminergic pathways offers indirect evidence. Voxel-based whole brain analysis showed that apart from SN/VTA, the NAcc, Ca and Hi were activated in both groups. BOLD activity in these areas has been previously correlated to dopamine levels using positron emission tomography (Schott et al., 2008), and they are known as target regions for dopaminergic projections originating in SN/VTA (Düzel et al.,

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Kommentar [7]: I don't understand.

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Gelöscht: one could expect a similar drop in the inverted feedback group, we cannot assume the BOLD response in SN/VTA is linearly correlated to the novelty of the reward.

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Kommentar [8]: And functional connectivity

2009). Therefore, the BOLD signal increases observed in our study may well reflect firing of dopaminergic neurons.

When using subject-wise measures of SCR as a covariate, we found a positive trend between SCR and SN/VTA activity in the veridical feedback group, which was significantly larger than that of the inverted feedback group. On one hand, this could mean that the visual feedback affects SCR, which could be an orienting response (Maltzman and Boyd, 1984). However, this appears unlikely because an orienting response should affect both groups in the same manner, which was not evident. On the other hand, another way of interpreting this differential correlation is that self-regulation of SN/VTA is associated with emotional arousal and/or valence. Previous work has shown a strong relationship of SCR with mental imagery, including correlations with emotional arousal and valence (McTeague et al., 2009, McTeague et al., 2010, McTeague et al., 2012). Thus, it is more likely that the differential correlation of SCR with SN/VTA activity is due to a stronger relationship of self-regulation of SN/VTA with emotional arousal rather than with orienting response.

Given the supposed habituation, one of the main limitations of this study is lack of a direct measure of cognitive fatigue. We did not find reductions in SCR, but did find activity in some associated brain regions. Yet without a separate measure, relating this activity to cognitive fatigue or habituation remains somewhat speculative. Understanding the dynamics of self-regulation, especially as it relates to the ability to learn, is crucial to the development of neurofeedback as a clinical tool. While there does appear to be some intrasession learning, further study would be necessary to

evaluate between session learning effects that other rtfMRI neurofeedback studies have shown (e.g. (Bray et al., 2007, Caria et al., 2007, Shibata et al., 2011)).

The SN/VTA is a difficult region to image (D'Ardenne et al., 2008), with challenges such as small size and proximity to the basilar artery leading to issues with magnetic susceptibility. It may be possible that neurofeedback from other regions along the dopaminergic pathways could be more effective. For instance, Subramaniam et al. have previously conducted a successful pilot study on Parkinson's patients using neurofeedback from the supplementary motor area, showing improved motor outcomes compared to controls with sham feedback (Subramanian et al., 2011). Another study by the same group used neurofeedback from target areas in the emotion network individually tailored to the subject, such as the amygdala and insula (Johnston et al., 2010). They found increased NAcc activity as a consequence of successful up-regulation. Other regions with a more direct connection to the SN/VTA could also have been used as targets, such as the striatum. However, the SN/VTA has the largest concentration of dopaminergic neurons (Francois et al., 1999) and as such, BOLD signal there may be more likely to represent dopaminergic activity (Düzel et al., 2009). In addition, the SN/VTA is the source of multiple dopaminergic pathways and therefore could have a wider impact. The fact that we found functional connectivity to increase between SN/VTA and ventral (veridical) as well as dorsal striatum (both groups) supports the validity of assumption, i.e., activation of dopaminergic pathways.

5 Conclusions

This study demonstrates that young healthy volunteers can voluntarily up-regulate

SN/VTA by imagining pleasant scenes and receiving online neurofeedback information about their SN/VTA activation. We found that SN/VTA can be self-regulated through imagery and that neurofeedback can assist in this regard. Further research is required to develop strategies for persistent regulation and investigate behavioral consequences. If successful, such strategies could have far reaching applications from the treatment of addiction to Parkinson's disease.

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Figure Captions

Figure 1

Anatomical localizer for SN/VTA. The three radiological views are centered on the SN/VTA, shown in detail in the inset on the bottom left.

Figure 2

Experimental protocol. Following an anatomical localizer, each participant was exposed to two conditions: imagery and imagery with neurofeedback. Alternating 20-second blocks of neutral and rewarding imagery composed each of the approximately six minute runs.

Figure 3

Results from Representative Subject in Veridical Feedback Group. In (a), SN/VTA activity is shown over runs for a representative veridical feedback participant, whereas a representative inverted feedback participant is shown in (b). Below, in (c), the time course of activity from the second neurofeedback run in the veridical feedback participant is shown along with according skin conductance response and example cardiac and respiration regressors (first order cosine), respectively.

Figure 4

Effect of Neurofeedback. Baseline-corrected SN/VTA beta values over all runs in the veridical feedback group compared to the inverted feedback group. Vertical lines indicate standard error. Results show a significantly larger increase between Run 1 and Run 2 in the veridical feedback group ($p < 0.05$), which is significantly larger compared to inverted feedback ($p < 0.05$). The veridical feedback group also showed an overall increase compared to baseline ($p<0.05$), whereas the inverted group did not ($p=0.26$).

Figure 5

Random-Effects GLM Analysis. Both the veridical (left) and inverted (right) feedback groups showed significant activation in SN/VTA and other reward regions. Both of the views show FDR-corrected ($p<0.05$) activity along the nigrostriatal pathway, from the SN/VTA to the dorsal caudate (Ca) to the precentral gyrus (PG). Table 1 provides a summary of other regions activated.

Figure 6

Functional Connectivity Analysis. Functional connectivity using a SN/VTA seed region, veridical (left), inverted (middle) and veridical > inverted (right) all cluster-level corrected, $p<0.05$, all cluster volumes > 320 mm^3. Both groups show increased connectivity in ventral and dorsal striatum. Veridical feedback group shows greater connectivity in dorsal striatum than inverted group. A summary is given in Table 2.

Figure 7

Differential correlations between SCR and SN/VTA depend on neurofeedback. When correlating the beta values of the subjects from the two groups with their corresponding SCR beta values, the veridical feedback group (dark) shows a positive trend with SN/VTA beta ($r = 0.45$, $p=0.12$), while the inverted feedback group (light) shows a negative trend ($r = -0.35$, $p=0.18$), significantly less than the veridical feedback group (ANCOVA, $p<0.05$).

Tables

Table 1

Summary of random effects analysis of both groups over whole brain (peak activation, FDR corrected, $p<0.05$, cluster volumes> 160 mm^3). No significant clusters were found when comparing groups.

Table 2

Summary of functional connectivity analysis over whole brain with SN/VTA seed (cluster-level corrected, $p<0.05$, all cluster volumes > 320 mm^3).

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